

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202133Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology and Biopharmaceutics Review

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NDA:	202133
Generic Name:	Fluoxetine
Brand Name:	TBD
Strength and Dosage Forms:	60 mg Tablet
Indication:	Treatment of Major Depressive Disorder
Sponsor:	Edgemont
Submission Type:	Original NDA (505 (b)(2))
Submission Date:	12/9/10, 3/31/11
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Joga Gobburu, Ph.D.

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### Executive Summary

#### Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 202133 and finds the data acceptable. OCP supports approval of fluoxetine 60 mg tablet for regimens in the approved indications for Prozac where the 60 mg dose is recommended.

#### Phase IV Commitment

None recommended

### Summary of Clinical Pharmacology and Biopharmaceutics Findings

#### *Regulatory Background*

This application was filed as a 505(b)(2) NDA. The sponsor is seeking indications approved for prozac capsules (refer to indications below). The application relies on the Agency's previous findings of safety and efficacy for fluoxetine (Prozac) capsules by Eli Lilly for these indications. Prozac immediate release capsules are currently available in 10mg, 20 mg and 40 mg strengths. Fluoxetine 60 mg strength is not currently available in the US. The sponsor intends to introduce Fluoxetine 60 mg tablets with this application because 60 mg/day is the recommended dose for bulimia nervosa in adults and is within the dosing range for other indications such as MDD, OCD and panic disorder (PD). And the 60 mg strength should improve compliance. Prozac tablets were approved in 1999 but were discontinued and are not currently marketed in the US. The discontinuation of Prozac tablets was not due to safety and efficacy reasons. Therefore, in the pivotal bridging bioequivalence studies, the reference listed drug (RLD) for the tablet, fluoxetine hydrochloride tablets (Mylan, ANDA 75755) was used as the reference drug. The RLD was demonstrated to be bioequivalent to Prozac (Eli Lilly) tablets.

*Proposed Therapeutic Indication and Dosage Regimen*

(b) (4) Major Depressive Disorder (MDD) in adult and pediatric patients

(b) (4) Obsessive Compulsive Disorder (OCD) in adult and pediatric patients aged 7 to 17 years

(b) (4) Bulimia Nervosa in adult patients

(b) (4) Panic Disorder with or without agoraphobia in adult patients

**Dosing**

MDD: Recommended initial dose of 10 - 20 mg/day in adult and pediatric patients. Adults (b) (4) dose of 20 to 80 mg/day

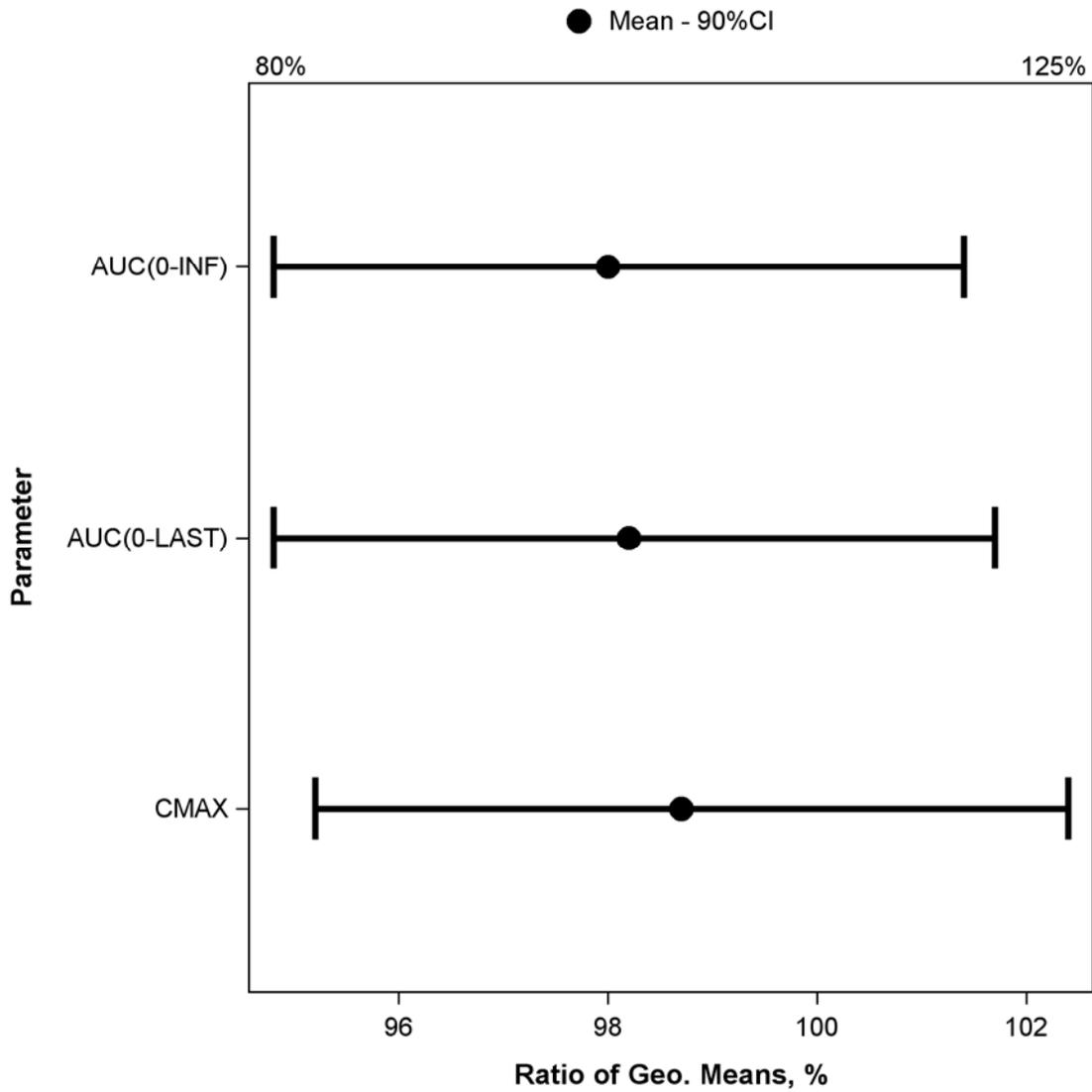
OCD: Recommended initial dose of 10 - 20 mg/day for adult and pediatric patients. Adult (b) (4) dose range of 20 to 60 mg

Bulimia Nervosa: Recommended dose of 60 mg/day

Panic Disorder: Recommended initial dose of 10 mg/day. Adult (b) (4) dose of 10 to 60 mg/day

*Bioequivalence of Fluoxetine tablets by Edgemont to Fluoxetine tablet by Mylan (RLD)*

Following a single dose administration of 1 x Fluoxetine 60 mg tablet and 3 x Fluoxetine 20 mg tablets (Mylan, RLD), Fluoxetine 60 mg (Edgemont) was demonstrated to be bioequivalent to 3 x Fluoxetine 20 mg tablets (Mylan), the reference listed drug. As shown in the following figure, the 90% confidence interval around the ratio of means for C<sub>max</sub> and AUC after administration of Fluoxetine 60 mg (Edgemont) and 3 x Fluoxetine 20 mg (Mylan) was contained within the 80% to 125% regulatory requirement for bioequivalence.



The reference for this 505(b)(2) is Prozac capsules. Fluoxetine 20 mg (Mylan) was demonstrated to be bioequivalent to Prozac 20 mg tablets (Prozac, Eli-Lilly) tablets in ANDA 075755. Fluoxetine (Prozac, Eli Lilly) tablet was demonstrated to be bioequivalent to Prozac capsule (NDA 20974). Therefore, Fluoxetine 60 mg tablets (Edgemont) would be equivalent to 3 x 20 mg Prozac capsules. The individual study report is provided in the Appendix.

The sponsor also demonstrated that Fluoxetine 60 mg tablets manufactured and marketed in Finland by Orion is bioequivalent to three of Fluoxetine 20 mg (Seronil) tablets manufactured and marketed in Finland by Orion Pharmaceuticals. The Fluoxetine 60 mg tablet (Orion) is similar to the proposed Fluoxetine 60 mg tablet that would be marketed in the US. In another study, the Fluoxetine 20 mg tablets (Orion) was demonstrated to be bioequivalent to Fluoxetine 20 mg capsules (Fontex) manufactured and marketed by Eli-Lilly in Finland. The quality and

quantitative (q &q) composition of Fontex could not be verified. Hence these results are supportive and not definitive. A brief summary of the legacy reports for these studies (451005 and 451001) are provided in the Appendix.

*What is Adverse Event profile in the pivotal bioequivalence study?*

Adverse events (AE) in the pivotal bioequivalence study are reported to have occurred in 15 to 21% of the subjects and was similar for each treatment arm. The AEs were reported to be mild and moderate and resolved without sequelae. The most common AE reported were headache, dizziness and nausea. The frequencies of these adverse events were similar between the treatment arms. The sponsor reported that two subjects (3 and 27) discontinued from the study due to AE. Subject no. 3 had elevated blood pressure (143/91 mmHg) which returned to 130/87 mmHg on the 60 day follow up evaluation. Subject 27 had absolute neutrophil count of  $10.6 \times 10^3/\mu\text{L}$  (normal range  $1-7 \times 10^3/\mu\text{L}$ ), neutrophil percent of 76.3% (normal range 50–70%) and WBC of  $13.9 \times 10^3/\mu\text{L}$  (normal range  $3-9.5 \times 10^3/\mu\text{L}$ ). Refer to Agency's medical review for detail safety evaluation. The AEs of increased white blood cell (WBC) count (Subjects 03 and 27, Treatment B) and elevated BP (Subject 03, Treatment B) were reported by the sponsor to be unlikely due to treatment given that they occurred at the end of the 6 week washout period between treatments.

#### **Office of Scientific Investigation (OSI) Inspection**

The Office of Scientific Investigation was requested by OCP to inspect the pivotal bioequivalence study (Study 101). Following the inspections of the clinical and analytical sites for study 101, OSI reported no significant findings were identified and recommended the study be accepted for review (refer OSI/DBGC report in DARRTS).

### **Label Recommendations**

#### **2 Dosage and Administration**

The following statements are recommended to be added to this section

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

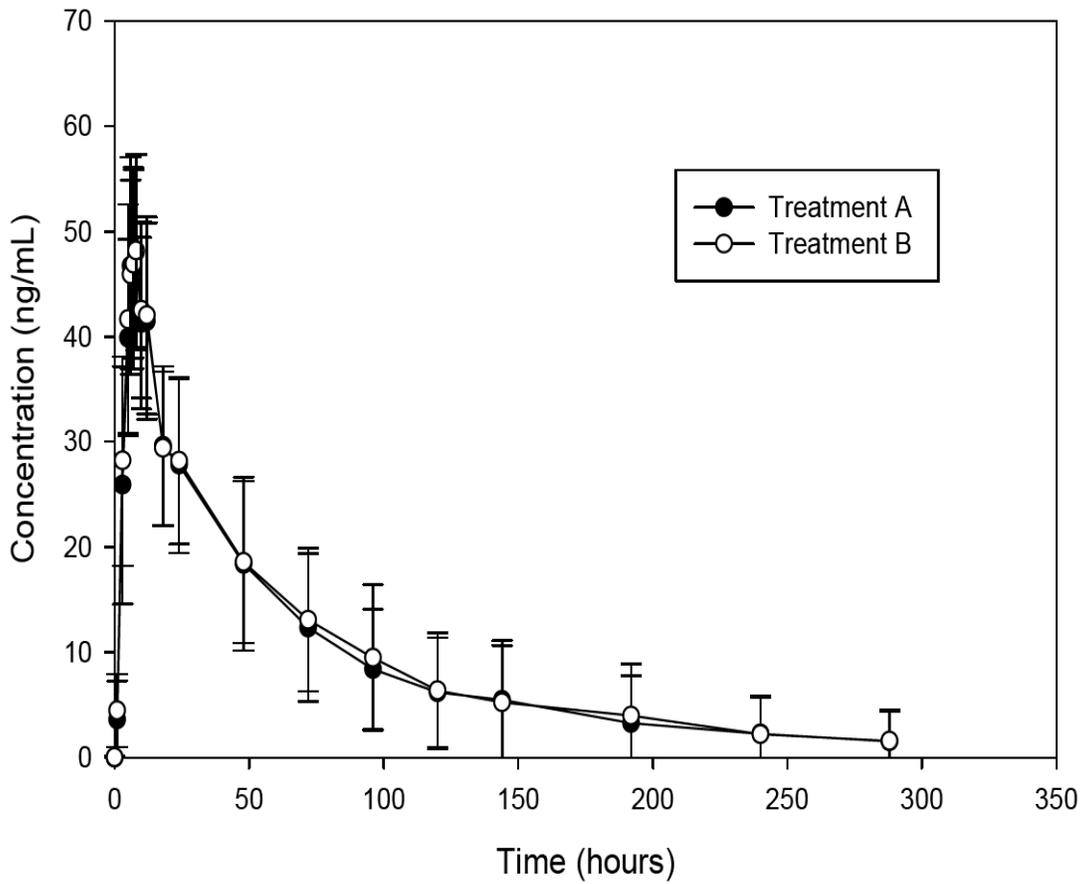
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## Appendix

### Individual Studies

#### Biopharmaceutics

<b>Report # 101</b>	<b>Study Period: 1/2</b>	<b>EDR Link</b> \\Cdsesub1\evsprod\nda202133
<b>Title</b>	A Randomized, Open-Label, Two-Period, Two Sequence, Single-Dose Crossover Study Comparing the Pharmacokinetic Profiles Following Oral Dosing of 1 x 60 mg Fluoxetine HCl Tablet to 3 x 20 mg Fluoxetine HCl Tablets in the Fasted State in Healthy Subjects	
<b>Study Design</b>		
<input checked="" type="checkbox"/> Bioequivalence		Bioavailability <input type="checkbox"/>
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Volunteers		
<b>Screening:</b> between day -21 to day -2	<b>Washout:</b> 42 days, outpatient	
<b>Period 1/2</b>	24-hr Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:	
<b>Treatments:</b> (Active Ingredient: Fluoxetine HCl). Administration: Fasting condition		
	<b>Test (A)</b>	<b>Reference (B)</b>
Dosage Form	Tablet	Tablet
Dosage Strength	60 mg	20 mg
Batch #.	MTYR3751	22349801
Administration	Oral	Oral
<b>Sampling Times (PK, plasma)</b>		
<ul style="list-style-type: none"> <li>• Test : 0 (pre-dose), 1, 3, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, 120, 144, 192, 288 hours post dose</li> <li>• Reference: 0 (pre-dose), 1, 3, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, 120, 144, 192, 288 hours post dose</li> </ul>		
<b>Analytical Method:</b> The performance of the analytical method is acceptable. Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>		
LC/MS/MS method validated over concentration range of 0.25 to 100 ng/mL. Average recovery of fluoxetine = 90%, QC Intraday precision range = 4.6% to 7.0%, QC Intraday Accuracy range = -9.2 to 1.2%, QC Interday Precision range = 3.9 to 11.2%, QC Interday Accuracy Range = -7.2 to 1.1%.		
<b>Statistical Method:</b> ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed. Pharmacokinetic metrics of fluoxetine and norfluoxetine estimated by noncompartmental methods.		
<b>Study Population :</b>		
Randomized/Completed/ Discontinued Due to AE	28/25/2 (# 3, 27) 2 AE DC: BP (143/91 mmHg), Hematocrit, hemoglobin, neutrophil (76%), elevated	
Age [Median (range)]	26.5 (18-40)	
Male/Female	20/8	
Race (Caucasian/Black/Asian/other)	24/4/0	
<b>Results</b>		



Summary of Mean ( $\pm$ SD) Fluoxetine Plasma Concentration

Treatment A = 1 x 60 mg fluoxetine tablet (Edgemont)

Treatment B = 3 x 20 mg fluoxetine tablets (Par)

**Summary of Mean ± SD Fluoxetine Pharmacokinetic Parameters**

Parameter	N	Test	Reference	Geometric Mean Ratio	90% CI
C <sub>max</sub> (ng/mL)	25	49.6 ± 10.0	50.2 ± 9.23	98.7	95.2 – 102.4
AUC <sub>t</sub> (ng*h/mL)	25	2750 ± 1510	2780 ± 1490	98.2	94.8 – 101.7
AUC <sub>∞</sub> (ng*h/mL)	25	3020 ± 1970	3060 ± 1980	98.0	94.8 – 101.4
T <sub>max</sub> (h)	25	7.20 ± 1.41	7.24 ± 1.48		
T <sub>1/2</sub> (h)	25	55.2 ± 36.9	53.8 ± 34.2		

**Summary of Mean±SD Norfluoxetine Parameters**

Parameter	N	Test	Reference	Geometric Mean Ratio	90% CI
C <sub>max</sub> (ng/mL)	23	24.7 ± 7.89	24.9 ± 8.25	99.98	97.0 – 103.0
AUC <sub>t</sub> (ng/mL*h)	23	5370 ± 1720	5380 ± 1670	100.03	98.1 – 102.0
T <sub>max</sub> (h)	23	74.6 ± 33.5	77.2 ± 28.9		
T <sub>1/2</sub> (h)	23	178 ± 61.7	178 ± 48.9		

**Site Inspected**

**Requested:** Yes  No

**Performed:** Yes  No  N/A

**Safety**

▪ Was there any death or serious adverse events?  Yes  No  NA

The sponsor reported that the AEs of increased white blood cell (WBC) count (Subjects 03 and 27, Treatment B) and elevated BP (Subject 03, Treatment B) that resulted in early discontinuation of these subjects from the study were unlikely due to treatment given that they occurred at the end of the 6 week washout period between treatments.

**Conclusion**

The regulatory criteria for establishing bioequivalence was met. Therefore, fluoxetine 1 x 60 mg tablets (Edgemont) is bioequivalent to 3 x 20 mg tablets (Par), used as the reference in this study. The exposure parameters for fluoxetine and norfluoxetine were within the 90% CI range of 80 to 125%. The sponsor reported Fluoxetine 60 mg tablets (Edgemont) were safe and well tolerated

**Comments**

*The reviewer agrees with the sponsor's conclusion that Fluoxetine 60 mg tablet (Edgemont) is bioequivalent to Fluoxetine 3 x 20 mg tablets (Par).*

Study 45101

<b>Report # 45101</b>		<b>Study Period: 1/2</b>		<b>EDR Link</b>	
<b>Title</b>		Bioavailability of Fluoxetine After a Single Oral Dose of 40 mg in Healthy Volunteers			
<b>Study Design</b>					
<input checked="" type="checkbox"/> Bioequivalence (Legacy Report)			<input type="checkbox"/> Bioavailability		
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Volunteers					
<b>Screening:</b> N/A			<b>Washout:</b> ≥ 28 days, outpatient		
<b>Period 1/2</b>		Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:			
<b>Treatments:</b> (Active Ingredient: Fluoxetine); Fasting conditions					
	<b>Test</b>		<b>Reference</b>		
Dosage Form	Seronil Capsules (Orion)		Fontex Capsules (Eli Lilly)		
Dosage Strength	20 mg		20 mg		
Batch #.	MTP-19-P02-01		67470VE		
Administration	Oral		Oral		
<b>Sampling Times (PK, plasma)</b>					
<ul style="list-style-type: none"> <li>• Test : 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 32, 48, 72, and 96 hours post dose</li> <li>• Reference: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 32, 48, 72, 96 hours post dose</li> </ul>					
<b>Analytical Method:</b> Gas chromatography/electron capture (GC/EC) Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>					
<b>Statistical Method:</b> ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed. PK parameters determined by non-compartmental methods. Analysis done using SAS					
<b>Study Population :</b>					
Randomized/Completed/ Discontinued Due to AE			15/14/0		
Age : 20 – 29 years			20- 29 years		
Male/Female			N/A		
Race (Caucasian/Black/Asian/other)			N/A		
<b>Results</b>					
<b>Parameter</b>	<b>N</b>	<b>Test</b>	<b>Reference</b>	<b>Geo Mean Ratio</b>	<b>90% CI</b>
AUC <sub>t</sub> (ng h/mL)	14	1034± 474	1043± 556	100.01	96.57 – 103.58
AUC <sub>∞</sub> (ng*h/mL)	12	996± 297	961± 259	100.61	96.12 – 106.32
C <sub>max</sub> (h)	14	29.6± 9.03	29.2± 8.73	100.37	95.94 – 106.01
<b>Site Inspected</b>					
<b>Requested:</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>			<b>Performed:</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/>		
<b>Safety</b>					
▪ Was there any death or serious adverse events? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA					
<b>Conclusion</b>					
Seronil 40 mg ( 2 x 20 mg capsules) was demonstrated to be bioequivalent to Fontex 40 mg ( 2 x 20 mg) capsules.					
<b>Comments</b>					
Based on the data provided, the reviewer agrees with the sponsor's conclusion Seronil 20 mg capsules (Orion) is bioequivalent to Fontex 20 mg capsules (Eli Lilly). This study was conducted in 1990 in Finland by Orion Pharmaceuticals. Edgemont stated that supplemental analysis was performed to confirm the results in the original report. Both the original report and the results of the supplemental analysis indicated that Seronil 20 mg is bioequivalent to Fontex 20 mg.					

Study 451005

<b>Report # 451005</b>	<b>Study Period:</b>	<b>EDR Link:</b> \\Cdsesub1\evsprod\nda202133\0000\m5			
<b>Title</b>	Bioavailability Study of Fluoxetine Comparing 60 mg Tablet and 20 mg Capsule After a Single Dose of 60 mg in Healthy Volunteers				
<b>Study Design</b>					
<input checked="" type="checkbox"/> Bioequivalence			<input type="checkbox"/> Bioavailability		
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Volunteers					
<b>Screening:</b> ≤ xx days		<b>Washout:</b> ≥ 42 days, outpatient			
<b>Period 1/2</b>		xx days, Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:			
<b>Treatments:</b> (Active Ingredient: Fluoxetine)					
	<b>Test</b>	<b>Reference</b>			
Dosage Form	Tablet (Orion)	Capsule (Seronil®, Orion)			
Dosage Strength	60 mg	20 mg			
Batch #.	MTV03-V18-03	VM010			
Administration	Oral	Oral			
<b>Sampling Times (PK, plasma)</b>					
<ul style="list-style-type: none"> <li>• Test : 0 (pre-dose), 1.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, 72, 100, 168 hours post dosing</li> <li>• Reference: 0 (pre-dose), 1.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, 72, 100, 168 hours post dosing</li> </ul>					
<b>Analytical Method:</b> The performance of the analytical method is acceptable. Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>					
Gas chromatography/electron capture (GC/EC)					
<b>Statistical Method:</b> ANOVA on natural log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed. Analyses use SAS for Windows Version 9.1.3 PK via non-compartmental methods					
<b>Study Population :</b>					
Randomized/Completed/ Discontinued Due to AE				22/20/0	
Age [Mean (±SD)]				24.2 ± 3.2	
Male/Female				11/12	
Race (Caucasian/Black/Asian/other)				Caucasian	
<b>Results</b>					
	<b>N</b>	<b>Test</b>	<b>Reference</b>	<b>Mean Ratio</b>	<b>90% CI</b>
AUC <sub>t</sub> (ng h/mL mg)	21	1806	1829	97.49	84.45 – 112.54
AUC <sub>∞</sub> (ng h/mL mg)	20	1815	1844	100.00	86.92 – 115.05
C <sub>max</sub> (ng/mL)	21	46.9	46.9	101.93	93.28 – 111.37
T <sub>max</sub>	21	6.52	6.57		
<b>Site Inspected</b>					
<b>Requested:</b> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>			<b>Performed:</b> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>		
<b>Safety</b>					
▪ Was there any death or serious adverse events? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA					
<b>Conclusion</b>					
Fluoxetine 60 mg (Orion) was demonstrated to be bioequivalent to 3 x 20 mg fluoxetine (Seronil) capsules. The 90% confidence interval was within the regulatory criteria for bioequivalence					
<b>Comments</b>					

*Reviewer agrees with sponsor's conclusion. This study was conducted in 1976 for regulatory authorities in Finland. Fluoxetine formulations used are not currently marketed in the US.*

APPEARS THIS WAY ON ORIGINAL

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/s/  
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KOFI A KUMI  
08/29/2011

JOGARAO V GOBBURU  
08/29/2011

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Addendum to Review#1</b>			
<b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 202-133	<b>Reviewer:</b> Minerva Hughes, PhD	
<b>Submission Date:</b>	9 Dec 2010		
<b>Division:</b>	Division of Psychiatry Products	<b>Team Lead:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Edgemont Pharmaceuticals	<b>Supervisor:</b> Patrick Marroum, PhD	
<b>Trade Name:</b>	Not proposed	<b>Date Assigned:</b>	15 Dec 2010
<b>Generic Name:</b>	Fluoxetine HCl Tablets USP	<b>Date of Review:</b>	2 May 2011 (Review #2)
<b>Indication:</b>	1. Major depressive disorder and obsessive compulsive disorder in adult and pediatric patients 2. Bulimia nervosa and panic disorder in adults	<b>Type of Submission:</b> Original NDA 505(b)2	
<b>Formulation/strengths</b>	Tablet/60 mg		
<b>Route of Administration</b>	Oral		
<p><b>SUBMISSION:</b> Edgemont Pharmaceuticals has submitted NDA 202-133 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of fluoxetine 60 mg scored tablets for the treatment of major depressive disorder and obsessive compulsive disorder in adults and pediatrics, and the treatment of bulimia nervosa and panic disorder in adults.</p> <p>This review provides an addendum to Biopharmaceutics Review #1 of 7 April 2011 and includes an assessment of the applicant's response to identified review issues.</p> <p><b>RESPONSES TO FDA COMMENTS:</b> As submitted in NDA Amendment of 27 April 2011.</p> <p>(b) (4)</p> <p>The USP dissolution requirements should be implemented for the quality control of fluoxetine tablets as follows:</p> <ul style="list-style-type: none"> <li>• Method - USP Apparatus 1 (basket) at 100 rpm using 1000 mL of 0.1N HCl</li> <li>• Limit – not less than (b) (4) (Q) is dissolved within 15 minutes.</li> </ul> <p>Submit a revised drug product specification sheet with the proposed changes to acknowledge your acceptance and commitment to implement this change prior to commercial manufacture.</p> <p><b>Applicant's Response:</b> Edgemont accepted the Agency's request and revised the specification accordingly.</p> <p><b>Reviewer's Comment:</b> Acceptable</p> <p>(2) Provide a copy of your disintegration method and verification report, including your rationale for the selected medium and the use of disks, if applicable.</p> <p><b>Applicant's Response:</b> Edgemont provided the method summary with reference to appropriate SOPs for calibration verification of the disintegration bath and testing per the principles of USP &lt;701&gt;</p> <p><b>Reviewer's Comment:</b> Acceptable</p> <p>(3) (b) (4)</p> <p>Please revise your disintegration</p>			

*specification to more appropriately reflect your batch history data and submit and updated drug product specification sheet. We recommend a specification limit of not more than (b) (4).*

**Applicant's Response:** Edgemont concurred with FDA's recommended specification and revised the disintegration specification accordingly.

**Reviewer's Comment:** Acceptable

**RECOMMENDATION:** From a Biopharmaceutics' perspective, the application is recommended for approval.

**Minerva Hughes**

Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick Marroum**

Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

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/s/  
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MINERVA HUGHES  
05/02/2011

PATRICK J MARROUM  
05/02/2011

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 202-133	<b>Reviewer:</b> Minerva Hughes, PhD	
<b>Submission Date:</b>	9 Dec 2010		
<b>Division:</b>	Division of Psychiatry Products	<b>Team Lead:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Edgemont Pharmaceuticals	<b>Supervisor:</b> Patrick Marroum, PhD	
<b>Trade Name:</b>	Not proposed	<b>Date Assigned:</b>	15 Dec 2010
<b>Generic Name:</b>	Fluoxetine HCl Tablets USP	<b>Date of Review:</b>	07 April 2011 (Review #1)
<b>Indication:</b>	1. Major depressive disorder and obsessive compulsive disorder in adult and pediatric patients 2. Bulimia nervosa and panic disorder in adults	<b>Type of Submission:</b> Original NDA 505(b)2	
<b>Formulation/strengths</b>	Tablet/60 mg		
<b>Route of Administration</b>	Oral		
<p><b>SUBMISSION:</b> Edgemont Pharmaceuticals has submitted NDA 202-133 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of fluoxetine 60 mg scored tablets for the treatment of major depressive disorder and obsessive compulsive disorder in adults and pediatrics, and the treatment of bulimia nervosa and panic disorder in adults. Fluoxetine tablets are film-coated capsule-shaped tablets that are scored on both sides and debossed with "FL 60" on one side. The tablet formulation contains 67.1 mg fluoxetine HCl, equivalent to 60 mg fluoxetine, and the excipients mannitol, corn starch, povidone, microcrystalline cellulose, magnesium stearate, (b) (4) and a film coat (b) (4).</p> <p>The drug product is manufactured by Orion Pharma who currently manufactures and markets this 60 mg dosage strength in Finland under the brand name Serionil.</p> <p>Fluoxetine 60 mg was first marketed in the US in 1999 under NDA 18-936 (Prozac) as a capsule; however, it was discontinued by the NDA holder, and there is currently no Fluoxetine HCl 60 mg single dose strength in the US.</p> <p><b>BIOPHARMACEUTIC INFORMATION:</b> In support of approval, NDA 202-133 includes the following biopharmaceutics data for review and evaluation:</p> <ul style="list-style-type: none"> <li>Proposed dissolution method and acceptance criteria, with justification</li> <li>Dissolution method development report</li> <li>Data on functionality of scored tablets</li> <li>Drug product stability data, including multi-point sampling and in-use (i.e., tablet splitting) data.</li> </ul> <p><b>RECOMMENDATION:</b></p> <p>The proposed dissolution method and acceptance criterion is not acceptable. The following deficiencies were identified, and should be conveyed to the applicant.</p> <ul style="list-style-type: none"> <li>(b) (4) The USP dissolution requirements should be implemented for the quality control of fluoxetine tablets as follows. <ul style="list-style-type: none"> <li>Method - USP Apparatus 1 (basket) at 100 rpm using 1000 mL of 0.1N HCl</li> <li>Limit – not less than (b) (4) (Q) is dissolved within 15 minutes.</li> </ul> </li> </ul> <p>Submit a revised drug product specification sheet with the proposed changes to acknowledge your</p>			

acceptance and commitment to implement this change prior to commercial manufacture.

- Provide a copy of your disintegration method and verification report, including your rationale for the selected medium and the use of disks, if applicable.

(b) (4)  
Please revise your disintegration specification to more appropriately reflect your batch history data and submit an updated drug product specification sheet. We recommend a specification limit of not more than (b) (4)

**Minerva Hughes**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Patrick Marroum**  
Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

## REVIEWER'S NOTES

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### 1.0 INTRODUCTION

#### 1.1 REGULATORY HISTORY

Edgemont Pharmaceuticals has submitted NDA 202-133 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of fluoxetine HCl 60 mg scored tablets in the treatment of major depressive disorder and obsessive compulsive disorder in adults and pediatrics and the treatment of bulimia nervosa and panic disorder in adults. Fluoxetine HCl was first approved in 1987 under NDA 018936 (Lilly, brand name Prozac) as a capsule dosage form. Several strengths were marketed under the NDA: 10 mg, 20 mg, 40 mg, and 60 mg; however, Lilly has discontinued marketing the 60 mg capsule strength, so no 60 mg dosage form exists on the US market. Other approved fluoxetine HCl dosage forms include oral solutions, tablets, and delayed release capsules.

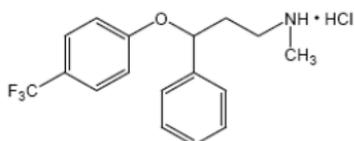
Previous regulatory correspondence was as follows.

- 3 Mar 2010, pre-NDA meeting held under PIND 107,525. FDA agreed to the applicant's overall approach for comparability assessments using in vitro dissolution in 1000 mL of medium, Apparatus I with sampling times of 5, 10, 15, 20, 30 min and requested that the NDA include the dissolution method development report.

#### 1.2 GENERAL DRUG SUBSTANCE CHARACTERISTICS

Fluoxetine HCl is supplied by Fermion Oy as a white to off-white crystalline powder. It is manufactured (b) (4). The melting point of the (b) (4) is approximately 158°C, and the average powder density is (b) (4). Polymorphs were not observed by X-ray powder diffraction and differential scanning calorimetry (DSC). The pH of a 1% aqueous solution of fluoxetine HCl is 4.5–6.5.

##### Structure:



Molecular formula: C<sub>17</sub>H<sub>19</sub>ClF<sub>3</sub>NO

Molecular weight: 345.79 g/mol

Aqueous solubility is pH dependent as illustrated in the table below.

pH	Solubility at 25 °C (mg/mL)
7.5	1.00
4.6	2.44
1.2	3.47

Source: As submitted in NDA, Table 2.3.S.1-2. Raw data submitted in (b) (4) Analytical Report, Section 3.2.P.2.1.

(b) (4)

### 1.3 GENERAL DRUG PRODUCT CHARACTERISTICS

The drug product, fluoxetine 60mg tablets, is an immediate release oral tablet containing 67.1 mg of fluoxetine HCl (equivalent to 60 mg fluoxetine base) per tablet. The tablets are capsule-shaped, scored on both sides, white film-coated, debossed with “FL 60” on one side (“FL” above the score and “60” below the score). The bulk drug product manufacturer is Orion Pharma located in Espoo, Finland. Primary product packaging, release, and stability testing will be performed at Patheon Puerto Rico Operations.

Tablet composition is summarized in the table below.

Ingredient	Reference to Quality Standard	Role	Quantity (mg/tablet)
(b) (4)			
Fluoxetine HCl	USP, Ph. Eur.	Active	67.1
Mannitol	USP/NF, Ph. Eur.	(b) (4)	(b) (4)
Maize Starch	USP/NF, Ph. Eur.		
Povidone (b) (4)	USP/NF, Ph. Eur.		
(b) (4)	USP/NF, Ph. Eur.		
Microcrystalline Cellulose (b) (4)	USP/NF, Ph. Eur.		
Magnesium Stearate	USP/NF, Ph. Eur.		
(b) (4)			(b) (4)
<b>Total weight</b>			<b>359</b>

Tablet manufacture involves (b) (4) - (b) (4) process steps. Product will be packed in 40 mL (30-count), white high density polyethylene bottles closed with a 28 mm child-resistant cap.

The tablet is intended to provide a single dose of 60 mg fluoxetine or 30 mg fluoxetine after tablet splitting

### 2.0 BIOPHARMACEUTICS QUALITY ASSESSMENT

## 2.1 DISSOLUTION METHOD DEVELOPMENT AND SPECIFICATION

Dissolution and disintegration testing is performed on the finished tablet. The proposed methods and specifications were as follows.

Test	Method	Specification	
		Release	Stability
Dissolution	USP Type I (Basket) 900 mL Water 100 rpm 37 ± 0.5°C Time: 20 minutes Profile: 5, 10, 20, 30, and 45 minutes	Q = (b) (4) in 20 min (S1 not less than (b) (4))	Q = (b) (4) in 20 min (S1 not less than (b) (4))
Disintegration	USP <701>, report min, max, and average	NMT (b) (4)	Not tested

The dissolution method was developed as part of the initial EU registration for fluoxetine tablet, 60 mg in Finland by Orion in 1996. The 1996 dissolution method development and validation report was included in the NDA for review. A rationale for medium, basket speed, and UV wavelength selection were included.

### Dissolution Medium Selection Study – Orion 1996 Report

Time min	0.1 N HCl		purified water		phosphate buffer pH 7.4	
	% released	S.D.	% released	S.D.	% released	S.D.
5	48.1	7.8	70.0	1.8	45.5	6.3
10	68.4	3.6	83.0	4.0	58.8	2.2
15	78.0	5.3	86.1	4.6	69.3	2.3
30	84.5	9.0	91.7	5.4	88.4	4.3
45	85.6	8.7	95.7	3.1	94.1	1.9

**Reviewer's Comment:** The dissolution apparatus and speed used for the medium selection study was not specified. Independent  $f_2$  analysis, using 0.1N HCl as the reference, show that the 0.1N HCl and purified water dissolution profiles are not similar ( $f_2 = 42$ ). Whereas, the 0.1N HCl and phosphate buffer dissolution profiles are similar ( $f_2 = 56$ ).

### Dissolution Basket Speed Selection Study – Orion 1996 Report

Time min	75 rpm		100 rpm		125 rpm	
	% released	S.D.	% released	S.D.	% released	S.D.
5	55.4	5.2	68.6	2.2	82.1	4.7
10	84.6	2.3	82.2	2.5	87.8	2.4
15	87.8	1.5	86.2	3.3	91.0	2.2
30	90.6	1.7	95.4	2.1	94.1	2.6
45	91.2	1.4	95.5	1.6	94.0	1.7

**Reviewer’s Comment:** *The dissolution medium used for the basket speed selection study was not specified. Dissolution was (b) (4) within 15 minutes, irregardless of the revolution speed.*

At the time of method development, the Pharmacopeial Forum (Vol 22:3, May-June 1996) suggested water for the dissolution medium for fluoxetine capsules; tablets were not described in any pharmacopeia. Based on the faster dissolution rates observed in water, and the pharmacopial reference, water was selected for the dissolution medium (refer to *The 1996 Orion Pharma Report Page 4(21)*). Similarly, 100 rpm was selected because it was most commonly used in compendia methods, and no differences were observed when a lower or faster speed was evaluated.

Quantitative analysis of dissolution samples used the same HPLC method as used for drug product Assay. Chromatographic conditions are summarized in the table below.

Table 3.2.P.5.2-3. HPLC Parameters for Fluoxetine 60mg Scored Tablets (Dissolution)	
HPLC Parameters	Values
Column	<u>Analytical:</u> Novapak Phenyl, 4 µm, 150 × 3.9 mm <u>Guard:</u> BrownLee New Guard Phenyl, 7 µm, 15 × 3.2 mm
Mobile Phase	30/70 Triethylamine buffer pH 5.5/Acetonitrile
Detection	UV at 225 nm
Flow Rate	1.0 mL/min
Injection Volume	10 µL
Retention Time	About 4 min

As submitted in the NDA.

The HPLC method was validated with respect to specificity, system suitability, linearity and range, quantitation limit and precision. Background effects from the tablet matrix were investigated with standard solutions in the range of 25% to 100% of fluoxetine. Analyte response was linear over the concentration range of 5-125% ( $r^2=1.000$ ). At the lower range of 5%, injection repeatability was <5%. The relative standard deviation for assay reproducibility was 5.7% at 30 minutes, which was the specification in 1996. Good day-to-day precision was also demonstrated. Transfer of the dissolution method to Patheon Puerto Rico Operations was completed to support final product release and stability testing. System suitability parameters at Patheon were met: peak resolution = (b) (4) injection repeatability RSD = (b) (4) and check standard (b) (4). In addition, lab to lab differences in mean dissolution results was 1.0%.

No information on the disintegration method was submitted for review.

**Reviewer Comment:** *Applicant should specify the disintegration medium used and clarify whether or not disks are used for the method. The medium is assumed to be water, since water is the medium of choice for dissolution; however, the analytical methods section does not adequately describe the disintegration test method. In addition, the applicant does not address any revalidation/verification studies completed since 1996 to support changes in the manufacturing process (raw material suppliers, equipment, etc.) that could impact the dissolution method. Of note, the dissolution time specification for release was tightened from (b) (4) to 20 minutes at Orion, but Orion’s stability specification remained not less than (b) (4) (Q) in 30 min. No information was submitted on when the change was implemented, but the method validation data from 1996 support a (b) (4) specification.*

## 2.2 JUSTIFICATION FOR DEVIATION FROM COMPENDIA DISSOLUTION METHOD

The applicant's proposed product name is Fluoxetine Tablet USP; however, they are requesting to keep the 1996 dissolution method (See Section 2.1), which deviates from the current compendia standard (USP 33-NF28) for fluoxetine tablets. The USP method is consistent with conditions used for rapidly dissolving substances and has a (b)(4) compared with the applicant's proposal.

### Fluoxetine Tablet USP Dissolution Method:

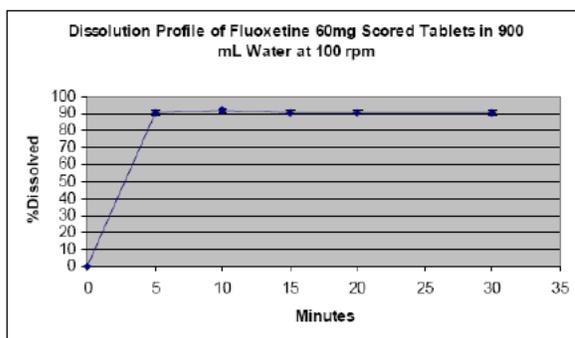
- USP Type I (Basket)
- 0.1N HCl, 1000 mL
- Limit: Not less than (b)(4)Q in 15 minutes

A comparative dissolution study was completed by Patheon (b)(4)

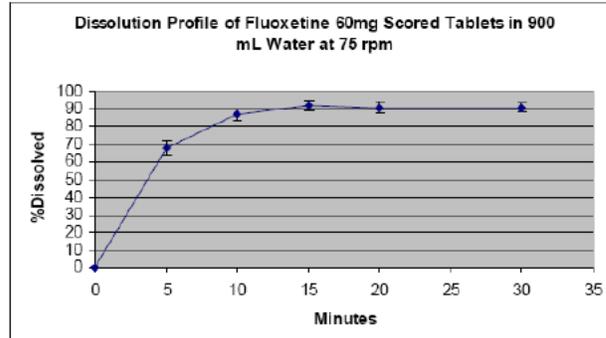
The study assessed the comparability of dissolution profiles for fluoxetine tablets, 60 mg under the following conditions using USP Apparatus 1 (N=12 for each run).

- Water, 900 mL at 100 rpm
- Water, 900 mL at 75 rpm
- 0.1N HCl, 1000 mL at 100 rpm
- 0.1N HCl, 1000 mL at 75 rpm
- 0.1N HCl, 900 mL at 100 rpm
- 0.1N HCl, 900 mL at 75 rpm
- pH 6.8 Phosphate Buffer, 900 mL at 100 rpm
- pH 4.5 Acetate Buffer, 900 mL at 75 rpm
- pH 4.5 Acetate Buffer, 900 mL at 100 mL

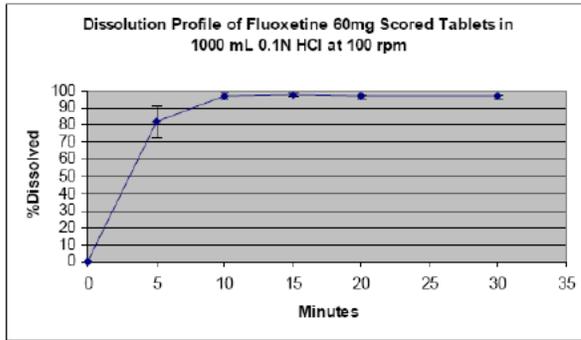
Dissolution profile data, as submitted in the NDA, are illustrated below for selected conditions.



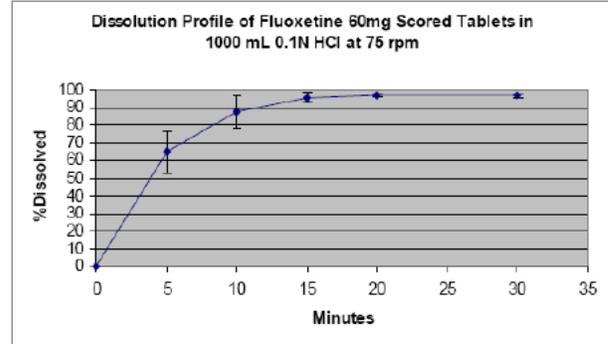
NDA Figure 3.2.P.2.2-1



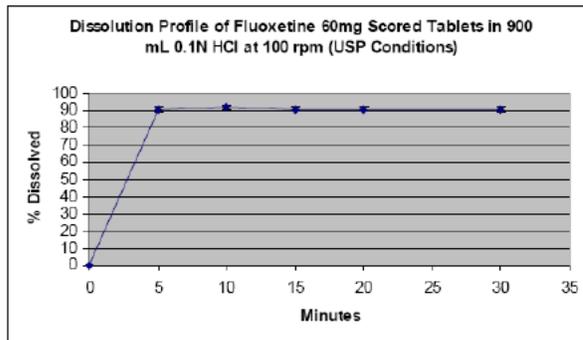
NDA Figure 3.2.P.2.2-2



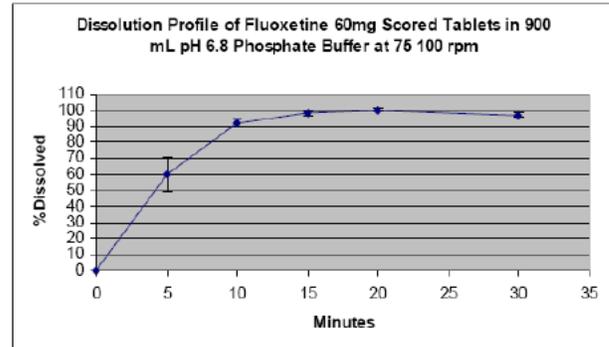
NDA Figure 3.2.P.2.2-3



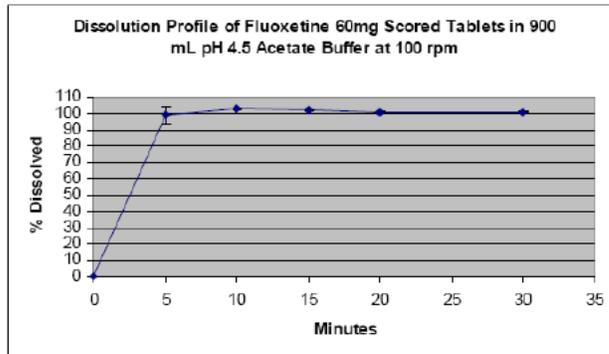
NDA Figure 3.2.P.2.2-4



NDA Figure 3.2.P.2.2-5



NDA Figure 3.2.P.2.2-7 (at 100 rpm)



NDA Figure 3.2.P.2.2-9

The data demonstrate that regardless of the dissolution medium used (water, 0.1N HCl, pH 4.5 or 6.8 buffer), the applicant's fluoxetine 60 mg tablets always met the criteria for a rapidly dissolving tablet (i.e., (b) (4) or more released within 15 minutes or less). Although the data show no appreciable difference in release rate, the applicant stated that as a quality control test, the proposed dissolution method is more discriminating than the USP method in demonstrating the immediate release characteristic of the batches.

**Reviewer's Comment:**

(b) (4)

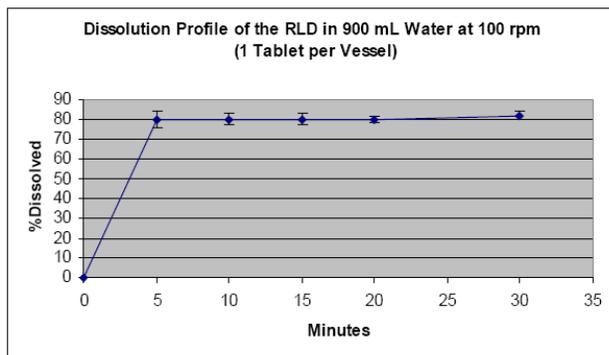
. The USP method is 1000 mL 0.1N HCl at 100 rpm.

Using water as the medium or 900 mL 0.1N HCl resulted in less than (b) (4) dissolution at 30 minutes or infinity (15 minutes post at 200 rpm), which is not optimal. Nevertheless, rapid dissolution was observed for both methods (i.e., (b) (4) in 15 minutes). Thus, neither the proposed method nor the USP method is sufficiently discriminating. Differences in dissolution behavior in different media that were observed during the 1996 Orion method validation work were not replicated in this dissolution method evaluation study conducted by Patheon. Of the methods, USP's tolerance limit is more reflective of the data with a specification of not less than (b) (4) (Q) in 15 minutes as compared to Edgemont's proposal of less than (b) (4). Additionally, the USP method also supports complete tablet dissolution. Consequently, the USP method is deemed most appropriate for tablet analysis.

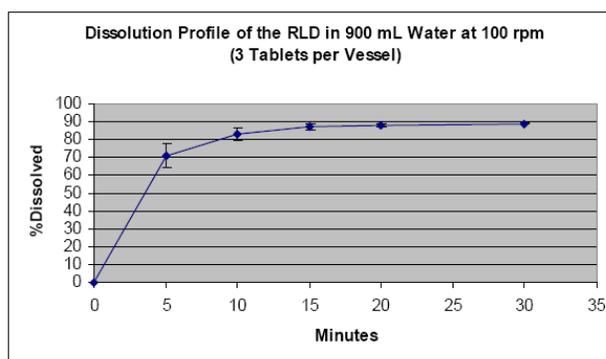
### 2.3 COMPARATIVE DISSOLUTION DATA – REFERENCE LISTED DRUG AND BATCH ANALYSIS DATA

The reference listed drug (RLD) used for studies was Par (Lot 22349801 manufactured for Par by (b) (4)). The applicant stated that the RLD is marketed under a Par label through a license agreement with the ANDA holder Mylan (ANDA 075755). [Reviewer's Note: ANDA 075755 is the RLD listed in the orange book for fluoxetine HCl tablets. The dailymed.nih.gov site confirms Mylan as the registrant and Par as the labeler for this ANDA. So, the Par product is the RLD for fluoxetine HCl tablets]

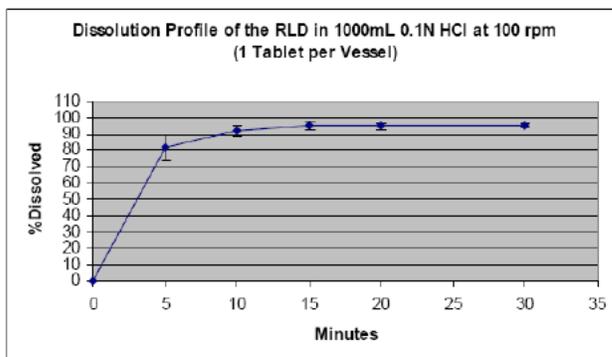
Comparative dissolution was studied using the USP recommended conditions of USP Apparatus 1 (basket) at 100 rpm in 1000 mL of 0.1N HCl, as well as Edgemont's proposed conditions of (b) (4). The study further compared the relative dissolution rates obtained when using 1 tablet per vessel to that obtained with 3 tablets per vessel (equivalent to 20 and 60 mg fluoxetine, respectively) in order to mimic the dosing regimen of the bioequivalence study.



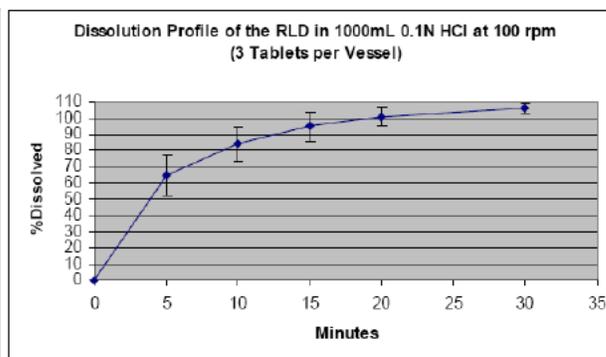
NDA Figure 3.2.P.2.2-10



NDA Figure 3.2.P.2.2-11



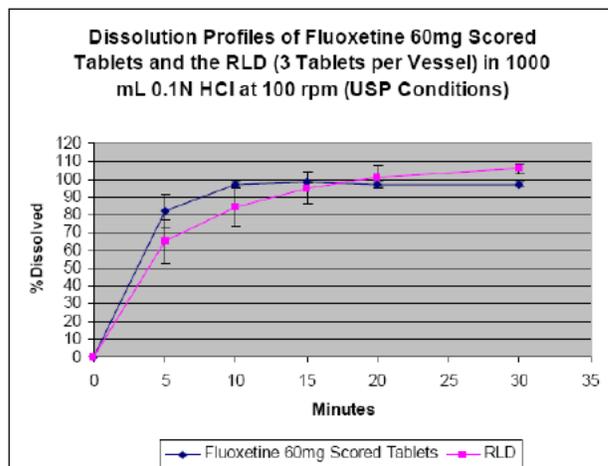
NDA Figure 3.2.P.2.2-12



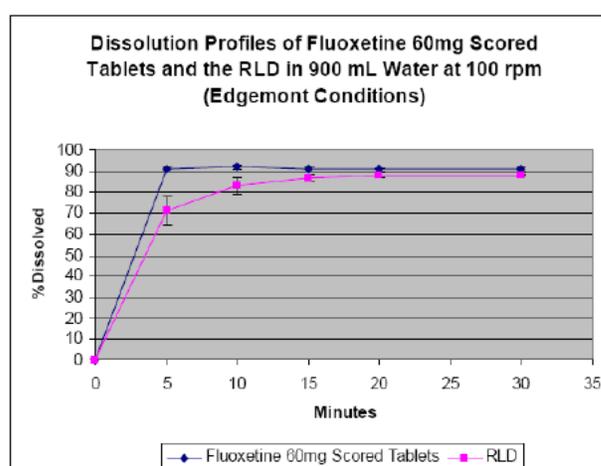
NDA Figure 3.2.P.2.2-13

The data demonstrate that the RLD, when tested per USP dissolution testing conditions, met the criterion for rapidly dissolving tablets (i.e., (b) (4) or more released within 15 min or less), regardless of whether 1 tablet per vessel or 3 tablets per vessel condition was tested. Unlike Edgemont's fluoxetine 60 mg tablets, the RLD fluoxetine 20 mg tablets did not meet the USP dissolution requirements when 1 tablet per vessel was studied using water as the medium.

Comparative dissolution data for the 3 tablet/vessel study are illustrated below.



NDA Figure 3.2.P.2.2-14



NDA Figure 3.2.P.2.2-15

Both fluoxetine HCl products achieved (b) (4) dissolution within 15 minutes when comparing the same amount of active per vessel (i.e., one 60 mg tablet versus 3 x 20 mg tablets).

**Reviewer's Comment:** Two different media was used for comparison: water and 0.1N HCl. The dissolution profiles were similar between the RLD and Edgemont's 60 mg fluoxetine tablet; however, incomplete dissolution of the RLD was observed for the 1 tablet/vessel and not the 3 tablet/vessel when water was used as a medium. Incomplete dissolution was also observed in other studies using the applicant's 60 mg tablet, so this observation seems to be related to water as the medium, although the applicant's data were not as pronounced as the 20 mg 1 tablet/vessel study. Despite this finding, (b) (4) of the 20 mg tablet was dissolved within 5 minutes, which is consistent with rapid dissolution regardless of the medium. (b) (4)

. Since

fluoxetine tablets are highly soluble and rapidly dissolving, the most appropriate method for quality control is the tolerance limits, which should be (b) (4) (Q) in 15 minutes. (b) (4)

Batch analysis data for registration and clinical batches are summarized in the table below.

**Release Data:**

		Released at Orion Pharma				Patheon Final Release of Lot 1321498
	Lot	1022948	1053228	1114423	1321498	MTYR 3751
	Manufacturing Date	Feb 2003	Mar 2004	Oct 2005	Jan 2010	Jan 2010
<b>Test</b>	<b>Specification</b>					
Disintegration	NMT (b) (4)					(b) (4)
Dissolution	Q = (b) (4) in 20 min S1 NLT (b) (4)					

Source: Section 3.2.P.5.4 Tables.

Stability data were submitted for one drug product lot (Lot MTYR3751) in the to-be-marketed packaging. The stability study is ongoing and 6 month's data were submitted in the initial NDA. Dissolution stability data are summarized below.

**Stability Data:**

Lot No.	Long-Term Storage 25°C Dissolution Average (Min, Max)		
	Initial	3 months	6 months
<b>MTYR3751 (Primary)</b>			
5 min	NS	70 (b) (4)	82 (b) (4)
10 min	NS	93 (b) (4)	93 (b) (4)
20 min	95 (b) (4)	91 (b) (4)	92 (b) (4)
30 min	NS	92 (b) (4)	91 (b) (4)
45 min	NS	91 (b) (4)	90 (b) (4)

NS = not sampled. Source: Section 3.2.P.8 Tables.

Supportive stability data were submitted for Orion manufactured and released product. After 36 months of storage at 25°C, mean dissolution at 30 minutes ranged from (b) (4) and disintegration times ranged from (b) (4)

Supporting stability batches were as follows.

Batch	Manufacture Date	Batch Size (Number of Tablets)	API Source	Packaging <sup>b</sup>	Long-Term Stability Data	Accelerated Stability Data
MTV03-V18-03	Feb 1996	(b) (4)	Fermion	75 mL	0, 3, 6, 7, 12, 14, 15, 16, 25, 36, 38	0, 3, 6, 7
TTV03-X02-08	Aug 1996	(b) (4)	Fermion	20 mL	0, 4, 6, 7, 8, 24, 28, 30, 38	0, 4, 6, 7, 8
AA 001	Jan 1999	(b) (4)	Fermion	20 mL	0, 12, 31	
BI 001	Sept 2000	(b) (4)	Fermion	75 mL	0, 11, 25	
CB 001	Feb 2001	(b) (4)	Fermion	75 mL	0, 12, 26	
1022948	Feb 2003	(b) (4)	Fermion	40 mL	0, 12, 24	
1053228	Mar 2004	(b) (4)	Fermion	40 mL	0, 12, 24	
1114423	Mar 2007	(b) (4)	Fermion	40 mL	0, 12, 24	

Batch	Manufacture Date	Batch Size (Number of Tablets)	API Source	Packaging <sup>b</sup>	Long-Term Stability Data	Accelerated Stability Data
1273446	Dec 2008	(b) (4)	Fermion	75 mL	0, 12	

<sup>a</sup> = Target commercial batch size is (b) (4)  
<sup>b</sup> = The HDPE bottle size is presented.

**Reviewer’s comment:** Supportive dissolution data from Orion batches were controlled by different dissolution limits and different primary packaging compared with the applicant’s NDA proposal. In addition, no dissolution profile data were submitted for the Orion batches to more adequately bridge the dissolution data. Nevertheless, the historical dissolution data support the conclusion that tablet dissolution is essentially complete within 30 minutes and little to no changes in dissolution is observed during long-term storage.

Batch release and stability data do not support a disintegration specification of not more than (b) (4) minutes. This limit exceeds the dissolution tolerance limit, and does not provide for adequate quality control. A specification of not more than (b) (4) minutes is recommended. Mean disintegration times for the single primary stability batch in the to-be-marketed was less than (b) (4) minutes; however, the historical Orion supportive data were included in the basis for the recommendation, and the upper limit for historical lots was (b) (4) minutes.

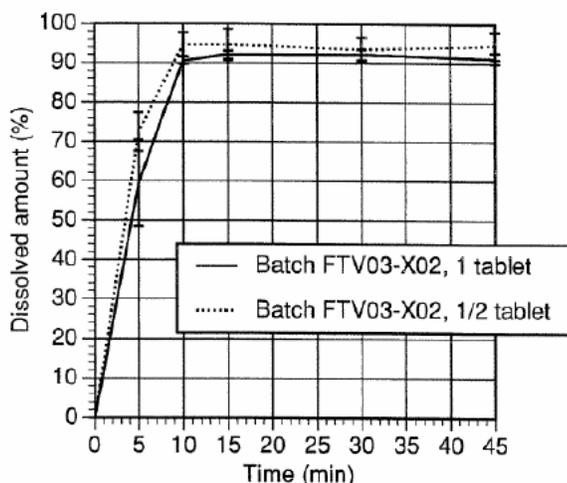
## 2.4 SUITABILITY OF TABLET SCORE FOR TABLET SPLITTING

The functionality of the scored tablet was assessed through content uniformity and dissolution testing of halved tablets during the original development of the Orion 60 mg tablet product in Finland. Tablet splitting was performed by gripping the tablet between the thumb and index finger of each hand and breaking. Content uniformity results for three batches were submitted (N = 20 tablets).

- Target: Whole Tablet – 359 mg; Half Tablet – 179.5 mg
- Batch MTV03-V18-03: mean = 180, % RSD = 2.8

- Batch MTV03-V19-03: mean = 179, % RSD = 2.0
- Batch MTV03-X01-03: mean = 181, %RSD = 2.8

Dissolution profile data for halved tablets compared with whole tablets, as analyzed by Orion, is summarized in the figure below.



NDA Figure 3.2.P.2.2-16.

The applicant also completed functionality testing of the scored tablets used in the bioequivalence study (i.e., primary registration batch) at Patheon. Tablets were split both manually and by using a tablet splitter. Assay, related substances, friability, and hardness were assessed in addition to dissolution and content uniformity.

Attributes relevant to this review are summarized below.

Test	Specification	Whole Tablet	Half Tablet (Using Splitter)	Half Tablet (Manual Splitting)
Assay	90.0-110.0 of label claim	(b) (4)	(b) (4)	Not available
Dissolution*	Q = (b) (4) in 20 min	(b) (4) at 20 min	5 min: 92 (b) (4) 10 min: 90 20 min: 90 30 min: 92 45 min: 92	5 min: 96 (b) (4) 10 min: 98 20 min: 98 30 min: 96 45 min: 98
Content Uniformity	USP <905>	(b) (4)	(b) (4)	(b) (4)
Friability	Report results			

\* A factor of 2X was applied to split tablets for dissolution analysis.

Half-tablet in-use stability (Protocol FLUO-0410A-00) was also evaluated after 8 weeks storage at 30°C/65% RH. Containers were opened and closed daily.

**Half Tablet (w/Splitter) Stability After 8 Weeks Storage - 30°C/65% RH**

Test	Whole Tablet	Half Tablet (Using Splitter)
Assay	(b) (4)	(b) (4)
Dissolution*	5 min: 85 (b) (4) 10 min: 94 20 min: 94	5 min: 94 (b) (4) 10 min: 94 20 min: 94

	30 min: 93 45 min: 93	(b) (4)	30 min: 94 45 min: 94	(b) (4)
Content Uniformity	(b) (4)			
Friability	(b) (4)			

\* A factor of 2X was applied to split tablets for dissolution analysis.

**Reviewer’s Comment:** *The functionality of the tablet score was adequately supported by dissolution, content uniformity and tablet weight loss data. Dissolution profile data were obtained using the proposed water-method and not the USP proposed method; however, based on the comparative dissolution data for the whole tablet, the dissolution profiles for half-tablets using the compendia method is expected to be similar.*

### 3.0 REGULATORY ISSUES AND COMMENTS FOR APPLICANT

The following comments should be conveyed to the applicant to address the review deficiencies noted.

1. Your rationale for deviating from compendia standards for the dissolution method and tolerance limits is not adequately supported by data. The USP dissolution requirements should be implemented for the quality control of fluoxetine tablets as follows.
  - Method - USP Apparatus 1 (basket) at 100 rpm using 1000 mL of 0.1N HCl
  - Limit – not less than (b) (4) (Q) is dissolved within 15 minutes.

Submit a revised drug product specification sheet with the proposed changes to acknowledge your acceptance and commitment to implement this change prior to commercial manufacture.
2. Provide a copy of your disintegration method and verification report, including your rationale for the selected medium and the use of disks, if applicable.
3. Your proposed disintegration specification of not more than 30 minutes is not supported by your data and the rapidly dissolving characteristics of your drug product. Please revise your disintegration specification to more appropriately reflect your batch history data and submit a revised specification sheet. We recommend a specification limit of not more than (b) (4).

**4.0 APPENDIX**

Dissolution data summary tables for Patheon lot MTYR 3751, as submitted in the NDA, for reference. Lot MTYR 3751 was used for bioequivalence studies.

**Table 5**  
**Dissolution Profile Fluoxetine 60mg Tablets, Lot MTYR3751**  
**in 900ml of Water at 100RPM**

Dissolution Profile Pull Times (minutes)						
Tablet No.	5	10	15	20	30	45 (200 RPM)
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Min%						(b) (4)
Max%						
Ave%	91	92	91	91	91	90
RSD%	1.4	1.2	1.1	1.0	1.7	0.8

Source: Patheon Comparative Dissolution Report.

**Table 7**  
**Dissolution Profile Fluoxetine 60mg Tablets, Lot MTYR3751**  
**in 1000ml of 0.1N HCl at 100RPM**

Dissolution Profile Pull Times (minutes)						
Tablet No.	5	10	15	20	30	45 (200 RPM)
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Min%	(b) (4)					
Max%	(b) (4)					
Ave%	82	97	98	97	97	96
RSD%	10.8	1.6	0.5	1.1	1.1	1.1

**Table 9**  
**Dissolution Profile Fluoxetine 60mg Tablets, Lot MTYR3751**  
**in 900ml of 0.1N HCl at 100RPM**

Dissolution Profile Pull Times (minutes)						
Tablet No.	5	10	15	20	30	45 (200 RPM)
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Min%	(b) (4)					
Max%	(b) (4)					
Ave%	91	92	91	91	91	90
RSD%	1.4	1.2	1.1	1.0	1.7	0.8

Source: Patheon Comparative Dissolution Report

**Table 11**  
**Dissolution Profile Fluoxetine 60mg Tablets, Lot MTYR3751**  
**in 900ml of Phosphate Buffer pH 6.8 at 100RPM**

Dissolution Profile Pull Times (minutes)						
Tablet No.	5	10	15	20	30	45 (200 RPM)
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Min%						(b) (4)
Max%						
Ave%	60	92	98	100	97	98
RSD%	18.3	2.6	0.9	1.2	1.2	1.4

Source: Patheon Comparative Dissolution Report.

**Table 12**  
**Dissolution Profile Fluoxetine 60mg Tablets, Lot MTYR3751**  
**in 900ml of Acetate Buffer pH 4.5 at 75RPM**

Dissolution Profile Pull Times (minutes)						
Tablet No.	5	10	15	20	30	45 (200 RPM)
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Min%						(b) (4)
Max%						
Ave%	69	104	103	102	102	102
RSD%	18.9	1.5	1.3	0.9	0.9	0.8

Source: Patheon Comparative Dissolution Report.

**Table 14**  
**FLUOXETINE 60 mg TABLETS**  
**Dissolution Comparative Study**  
**Lot MTYR3751**  
**Average Results of 12 Tablets**

Dissolution Medium	Water				0.1N HCl								Acetate Buffer pH 4.5				PO4 Buffer pH 6.8	
	100		75		100		75		100		75		100		75		100	
Basket Revolutions (RPM)	100		75		100		75		100		75		100		75		100	
Volume (mL)	900		900		1000				900				900				900	
Results Avg% & RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%	Avg%	RSD%
Time (min.)																		
0	0		0		0		0		0		0		0		0		0	
5	91	1.4	68	6.4	82	10.8	65	18.1	84	13.2	71	6.4	99	5.5	69	18.9	60	18.3
10	92	1.2	87	3.5	97	1.6	88	10.3	99	0.9	94	3.5	103	0.6	104	1.5	92	2.6
15	91	1.1	92	3.0	98	0.5	96	3.0	99	1.1	98	3.0	102	0.5	103	1.3	98	0.9
20	91	1.0	91	3.3	97	1.1	97	0.8	99	1.0	98	3.3	101	0.7	102	0.9	100	1.2
30	91	1.7	91	3.8	97	1.1	97	1.1	99	0.7	98	4.8	101	0.7	102	0.9	97	1.2
45 (200 RPM)	90	0.8	92	2.7	96	1.1	97	1.1	98	0.9	97	2.7	101	0.6	102	0.8	98	1.4

Source: Patheon Comparative Dissolution Report.

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MINERVA HUGHES  
04/07/2011

PATRICK J MARROUM  
04/07/2011

<b>BIOPHARMACEUTICS FILING REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 202-133	<b>Reviewer:</b> Minerva Hughes, PhD	
<b>Submission Date:</b>	9 Dec 2010		
<b>Division:</b>	Division of Psychiatry Products	<b>Team Lead:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Edgemont Pharmaceuticals	<b>Supervisor:</b> Patrick Marroum, PhD	
<b>Trade Name:</b>	Not proposed	<b>Date Assigned:</b>	15 Dec 2010
<b>Generic Name:</b>	Fluoxetine Tablets USP	<b>Date of Review:</b>	24 Jan 2011
<b>Indication:</b>	1. Major depressive disorder and obsessive compulsive disorder in adult and pediatric patients 2. Bulimia nervosa and panic disorder in adults	<b>Type of Submission:</b> Original NDA 505(b)2	
<b>Formulation/strengths</b>	Tablet/ 60 mg		
<b>Route of Administration</b>	Oral		
<p><b><u>SUBMISSION:</u></b> Fluoxetine HCl is a potent and selective inhibitor for presynaptic uptake of serotonin in the central nervous system with antidepressant activity. The drug substance was first approved by FDA in 1987 as Prozac, NDA 18-936 sponsored by Eli Lilly. A 60 mg capsule was introduced to the market in 1999; however, Eli Lilly discontinued marketing Prozac 60 mg capsules, and there is currently no 60 mg Fluoxetine single dose strength in the US. Edgemont Pharmaceuticals has submitted NDA 202-133 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of fluoxetine 60 mg scored tablets in the same indications as the innovator Prozac; treatment of major depressive disorder and obsessive compulsive disorder in adults and pediatrics, and the treatment of bulimia nervosa and panic disorder in adults.</p> <p>Fluoxetine tablets USP, 60 mg are film-coated capsule-shaped tablets that are scored on both sides and debossed with "FL 60" on one side. The tablet formulation includes the excipients mannitol, corn starch, povidone, microcrystalline cellulose, magnesium stearate, (b)(4) and a film coat (b)(4)</p> <p>The proposed fluoxetine tablets, 60 mg are manufactured by Orion Pharma who currently manufactures and markets this dosage strength in Finland.</p> <p><b><u>BIOPHARMACEUTIC INFORMATION:</u></b> In support of approval, NDA 202-133 includes the following biopharmaceutics data for review and evaluation:</p> <ul style="list-style-type: none"> <li>• Proposed dissolution method and acceptance criteria, with justification</li> <li>• Dissolution method development report</li> <li>• Data on functionality of scored tablets</li> <li>• Drug product stability data, including multi-point sampling and in-use (i.e., tablet splitting) data.</li> </ul> <p><b><u>RECOMMENDATION:</u></b> From a biopharmaceutics perspective, the NDA is considered fileable. There is sufficient biopharmaceutics data to permit a substantive review.</p> <p><b><u>Minerva Hughes</u></b> Biopharmaceutics Reviewer, ONDQA</p> <p><b><u>Patrick Marroum</u></b> Biopharmaceutics Supervisor, ONDQA</p> <p><i>cc: Angelica Dorantes, Mohan Sapru, Hiren Patel</i></p>			

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MINERVA HUGHES  
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